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Somatomedin-C as a fetal growth promoting factor and amino acid composition of cord blood in Japanese neonates

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1 Introduction

Fetal growth is exponential, and the mechanisms that regulate fetal growth in humans is poorly understood. It has been suggested that fetal growth is influenced by genetic, nutritional, environmental, uteroplacental and fetal factors [11]. In Japan, the fetal growth retardation and low birth weight infants make up about 10 percent of all deliveries, and their morbidity and mortality are very high in comparison with normal babies.

From a clinical point of view, to reduce the incidence of intrauterine growth retardation, we introduced maltose-infusion therapy and have had good clinical results in increasing fetal weight and decreasing neonatal hypoglycemia. We found decreased levels of aspartic acid in umbilical arterial blood and increased levels of phenylalanine in umbilical venous and arterial blood. These results suggested that the clinical efficiency of maltose-infusion therapy was based not only on the increased supply of glucose but also on the efficient use of transported amino acid in the fetus [7].

Therefore as information concerning the mechanisms regulating normal fetal growth enables us to prevent or to treat growth retardation, in this paper an attempt was made to investigate the mechanism of growth promoting action of somatomedin-C, which is one of the most popular growth factors [9], in relation to the amino acid composition of umbilical venous blood and several parameters of the neonate.

Curriculum vitae

MITSUSHIGE NISHIJIMA *received his medical degree from the Iwate Medical University in Morioka, Japan, in 1974. After chief residency at the Hachinohe Red Cross Hospital in 1979, he worked in Iwate Prefectural Hospital as the chief resident. In 1980, he was appointed chief resident of the perinatal unit of the Obstetrics Department of Iwate Medical University. In 1985 he was appointed Dozent. His main research interest are in the field of perinatal medicine, especially fetal growth.*

2 Materials and methods

Blood samples from the umbilical vein were obtained from 28 cases. They were withdrawn into disposable syringes and distributed to vessels containing EDTA for the analysis of amino acids and somatomedin-C, respectively. All blood samples were centrifuged immediately at 3000 rpm for 20 minutes. They were then transported to separate vessels, and kept in a frozen

state at −70 °C until analysis. The sera were deprotenized with sulfosalicylic acid (20%), and amino acid analysis of 20 specimens were performed with two-column ion exchange chromatography using an automatic amino acid analyzer (Hitachi, model 835). Levels of somatomedin-C were determined by radioimmunoassay (Nichols Institute, USA). Evaluation of fetal growth was based upon NISHIDA's intrauterine growth curve for Japanese neonates [6].

Statistical significance was assessed using Mann-Whitney U test to make inter-group comparisons. The linear correlation coefficient, the slope, the intercept and the significance level were evaluated with the Statistical Package for Social Science (SPSS) of Northwestern University. Abnormal values were treated by Grubb's method.

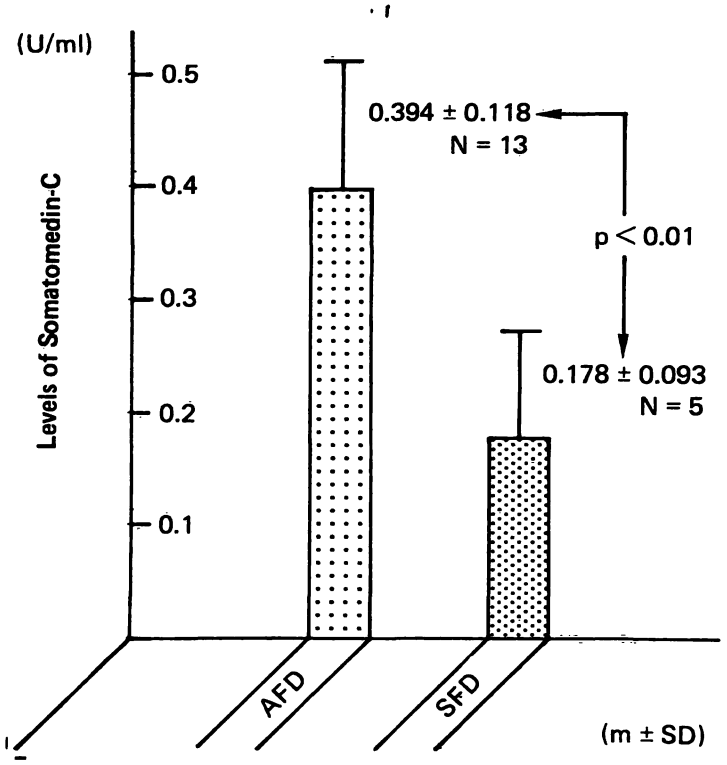

Figure 1. Somatomedin-C in cord blood of full term pregnancy of appropriate for date babies (AFD) and small for date babies (SFD).

3 Results

The comparison of mean value of somatomedin-C between appropriate for date (AFD) babies and small for date (SFD) babies in full term pregnancy showed significantly higher levels in AFD babies (figure 1).

We also evaluated other parameters of the neonate (birth weight, birth length, head circumference, chest circumference and Kaup index [× 10]) in AFD babies (table I). But only the birth weight in the physical parameters of the neonate (figure 2) and the placental weight for AFD babies including full term and preterm pregnancy had significant positive correlations with the level of somatomedin-C in cord blood (table I).

The mean and the standard deviation of amino acids in umbilical venous blood are presented in table II, but the comparison of mean value of each amino acid between AFD babies and

Table I. Correlations between the level of somatomedin-C in cord blood and physical parameters of the neonate including placental weight.

	n	r	p
Somatomedin-C vs. birth weight	19	0.556	< 0.02
Somatomedin-C vs. birth length	14	0.123	n. s.
Somatomedin-C vs. head circumference	14	0.184	n. s.
Somatomedin-C vs. chest circumference	14	0.387	n. s.
Somatomedin-C vs. Kaup index (× 10)	14	0.451	n. s.
Somatomedin-C vs. placental weight	18	0.595	< 0.01

Note: All these data were obtained from appropriate for date babies including full term and preterm babies, but birth weight of one case for preterm appropriate for date baby was omitted due to inappropriate date of measuring the birth weight.

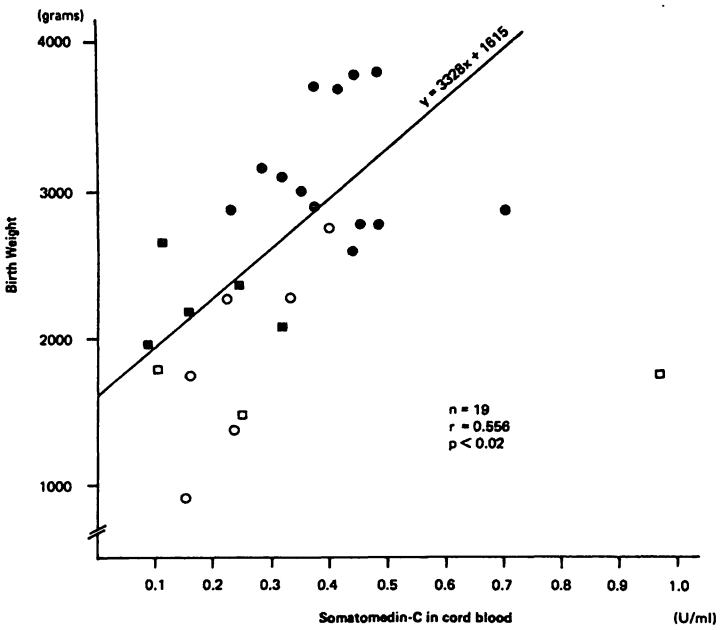

Figure 2. Relationship between the level of somatomedin-C in cord blood and birth weight of appropriate for date babies for full term (●) and preterm (○) deliveries. Cases with small for date babies also indicated for full term pregnancies (■) and for preterm pregnancies (□).

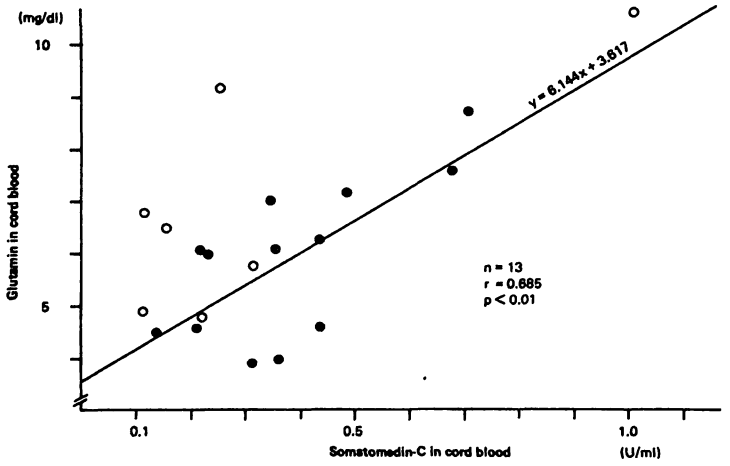

Figure 3. Relationship between the level of somatomedin-C in cord blood and the concentration of glutamin in cord blood of appropriate for date babies (indicated with closed circles). Open circles indicate cases with small for date babies.

SFD babies showed no significant difference in this series.

Of the 40 amino acids and their analogues, somatomedin-C for AFD babies had significant positive correlation with glutamine ($r = 0.685$, $p < 0.01$, figure 3), proline ($r = 0.657$, $p < 0.02$), asparagine ($r = 0.590$, $p < 0.02$), methionine ($r = 0.575$, $p < 0.02$), isoleucine ($r = 0.574$, $p < 0.03$) and ethanolamine ($r = 0.711$, $p < 0.01$). While significant negative correlation was found only tryptophane and somatomedin-C ($r = -0.555$, $p < 0.03$, figure 4) (table III).

Table II. The means and their standard deviations of amino acid concentration in cord blood in AFD and SFD babies.

Amino acid	AFD (n = 13)	SFD (n = 7)	Amino acid	AFD (n = 13)	SFD (n = 7)
Taurine	2.43 ± 0.77	2.74 ± 0.55	Cystine	0.19 ± 0.14	0.23 ± 0.10
Aspartic acid	0.14 ± 0.09	0.14 ± 0.09	Methionine	0.46 ± 0.11	0.47 ± 0.09
Hydroxy Prolin	0.42 ± 0.13	0.37 ± 0.04	Isoleucine	0.94 ± 0.28	0.95 ± 0.14
Threonine	2.78 ± 0.96	3.05 ± 0.92	Leucine	1.63 ± 0.52	1.72 ± 0.30
Serine	1.74 ± 0.32	1.75 ± 0.17	Tyrosine	1.41 ± 0.43	1.39 ± 0.37
Asparagine	0.95 ± 0.30	1.02 ± 0.17	Phenylalanine	1.49 ± 0.38	1.44 ± 0.30
Glutamic acid	1.56 ± 1.13	1.29 ± 0.95	Ethanolamine	0.25 ± 0.11	0.19 ± 0.04
Glutamine	5.91 ± 1.52	7.03 ± 2.33	Ornithine	1.15 ± 0.36	1.19 ± 0.31
Proline	2.21 ± 0.52	2.11 ± 0.39	Tryptophane	1.16 ± 0.37	1.16 ± 0.43
Glycine	1.82 ± 0.37	1.91 ± 0.37	Lysine	4.96 ± 1.24	5.45 ± 1.52
Alanine	4.31 ± 1.39	4.20 ± 1.20	Histidine	1.65 ± 0.35	1.61 ± 0.47
Citrulline	0.16 ± 0.05	0.15 ± 0.04	3-Methylhistidine	0.09 ± 0.05	0.11 ± 0.05
A−A. B. A.	0.17 ± 0.07	0.18 ± 0.07	Arginine	1.08 ± 0.43	1.36 ± 0.32
Valine	2.80 ± 0.75	2.96 ± 0.64	NH_3	0.44 ± 0.14	0.44 ± 0.21

Note: AFD: Appropriate for date babies, SFD: Small for date babies, A−A. B. A.: Alpha-Amino-n-butyric acid. One case of proline in both groups and one case of ethanolamine (mean ± S. D., mg/dl) in SFD group were rejected due to their abnormalities.

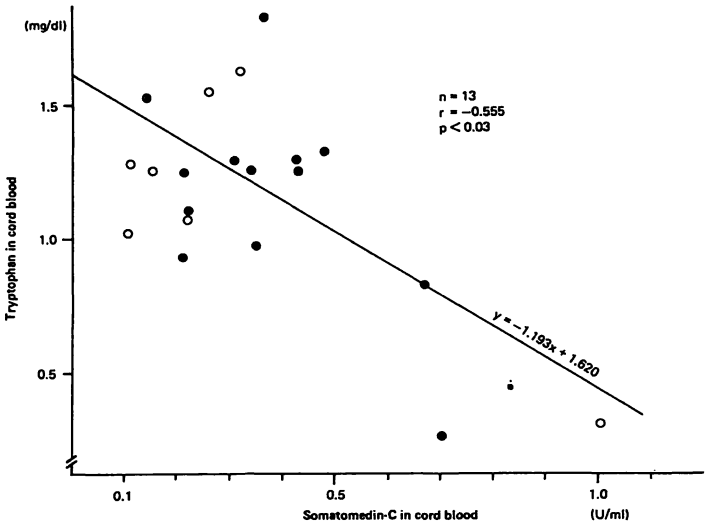

Figure 4. Relationship between the level of somatomedin-C in cord blood and the concentration of tryptophane in cord blood of appropriate for date babies (indicated with closed circles). Open circles indicate cases with small for date babies.

In small for date babies, the evaluation of the linear regression analysis of each amino acid and their analogues in relation to somatomedin-C revealed that only glutamine ($r = 0.764$, $p < 0.03$, figure 3) demonstrated a significant positive correlation, but also revealed that tryptophane showed a significant negative correlation ($r = -0.737$, $p < 0.03$, figure 4) not only in AFD babies but also in SFD babies. As for the methionine somatomedin-C correlation, there was an almost significant trend ($r = 0.662$, $p < 0.052$) for the SFD babies (table III).

4 Discussion

Somatomedin-C is a basic polypeptide and although not yet fully characterized, bears striking similarities to insulinlike growth factor. In differentiated cells such as fat and muscle, the somatomedins stimulate glucose and amino acid uptake, glycolysis, and protein synthesis [10]. A very reliable specificity can be achieved with radioimmunoassay which has recently been developed for all somatomedins [10].

The demonstration of the significant positive correlation between somatomedin-C and birth weight in AFD babies suggests a role for somatomedin-C in the control of normal fetal growth. Similar findings have been reported by KASTRUP et al [5] and GLUCKMAN et al [3], who also found a positive correlation not only with birth weight but also with body length and head circumference.

Our observation of the significantly lower level of somatomedin-C in growth retarded babies in comparison to AFD babies in full term pregnancy has confirmed the importance of somatomedin-C for the adequate fetal growth in utero, and it agrees with the report of FOLEY et al [2] in which the somatomedin activity as measured by the simultaneous incorporation of ^{35}S-sulphate and ^{3}H-methyl thymidine into costal cartilage from hypophysectomised rat. We also obtained a significant positive correlation between somatomedin-C and placental weight for AFD babies. This correlation appeared not to be present in SFD babies. KASTRUP et al [5]

Table III. Correlations between somatomedin-C and amino acids.

	AFD (n = 13)		SFD (n = 7)	
	r	p	r	p
Glutamine	0.685	< 0.01	0.764	< 0.03
Methionine	0.575	< 0.02	0.662	< 0.052
Proline	0.657	< 0.02	0.567	n. s.
Asparagine	0.590	< 0.02	− 0.148	n. s.
Isoleucine	0.574	< 0.03	− 0.148	n. s.
Ethanolamine	0.711	< 0.01	0.256	N. S. (n = 6)
Tryptophane	− 0.555	< 0.03	− 0.737	< 0.03

Note: AFD: Appropriate for date babies, SFD: Small for date babies. One case of proline in both groups was rejected due to its abnormality.

reported no significant correlation between cord somatomedin, which was determined by chick embryo assay, and placental weight. D'ERCOLE and UNDERWOOD [1] observed a correlation of placental weight with somatomedin-C.

This is the first report, to our knowledge, concerning the relationship between somatomedin-C and amino acid in human fetuses. Our data demonstrated four correlations which were significantly positive for AFD babies, but the correlation does not exist for SFD babies. This change of proline could be a suggestion of metabolic disturbances in proline components of collagen in growth retarded fetuses, because normally, proline with hydroxy proline constitutes 2/3 of the amino acid component of collagen. Since the mean value of any amino acid from AFD babies did not show any significant difference from that of SFD babies (which is in agreement with the report of PRENTON and YOUNG [8]), these changes of amino acids correlations including proline could not be explained clearly. There also seems to be many other problems to be clarified: the change of sensitivity to somatomedin-C of each organ and of each tissue during fetal development.

Our results also demonstrated a constant positive correlation between somatomedin-C and glutamine (main source of proline in almost all mammals) and the constant negative correlation between somatomedin-C and tryptophane. The continuity of positive correlation seemed to be found also in the relationship between somatomedin-C and methionine, which is the precursor of 1,3-diaminopropane that constitutes a part of spermidine and spermine.

Is there any possible explanation for the constant correlations for these three amino acids in relation to somatomedin-C? It is easy to identify these correlations were pseudo-relations. On the basis of the fact that hepatic tryptophane hydroxylase to the hydroxy derivatives is analoguous to the conversion to tyrosine from phenylalanine, and on the basis of significantly higher levels of phenylalanine on the fetal side, (but not the extent of maternal phenylketonuria) with maltose infusion during the therapy for intrauterine fetal growth retardation, this appears to be one of the possible keys of explaining these relationships, especially for tryptophane. Incidentally it should be noted that tryptophane pyrrolase which catalizes tryptophane kynurenic acid is inactive during fetal life.

Since the regulation of somatomedins, which was originally thought to be done solely by growth hormone, has proved to be sufficiently complex that nutrition and various hormones, such as insulin, exert a partial control [4], it is difficult to have a simple explanation for these results.

While our subject population was rather small and many details of these relationships are not clear, the results of this report lead us to speculate that somatomedin-C as a growth promoting factor in the fetus has some relationship with metabolites of tryptophane, for example serotonin and or melatonine, in regulating fetal growth in utero.

A follow up study to investigate these speculations with better experimental models and with more parameters is now in progress.

Summary

A study was undertaken to determine the relationship of somatomedin-C as a growth promoting factor to amino acid composition of umbilical venous blood in relationship to fetal growth.
In full term pregnancy somatomedin-C from cases with appropriate fetal growth was greater than those with fetal growth retardation. Within the physical parameters of the neonate only birth weight of appropriate for date babies had significant positive relationship to somatomedin-C in cord blood. Of the 40 amino acids and their analogues, significant positive correlations were found for glutamine, prolin, asparagin, methionin, isoleucin and ethanolamine in relation to the level of somatomedin-C, while a significant negative correlation was found between tryptophane and somatomedin-C of appropriate for date babies. In cases with fetal growth retardation, the evaluation of amino acid-somatomedin-C relationship revealed that glutamine demonstrated a sig-

nificant positive correlation and tryptophane demonstrated a significant negative correlation.
While many details of these relationships are not clear, the results of this report lead us to speculate that somatomedin-C as a growth promoting factor in the fetus has some relationship to metabolites of tryptophane, for example serotonine and or melatonine, in regulating fetal growth in utero.

Keywords: Amino acid, fetus, growth factor, somatomedin-C.

Zusammenfassung

Somatomedin-C als wachstumsfördernder Faktor beim Feten und Aminosäurespektrum im Nabelschnurblut bei japanischen Neugeborenen
In der vorliegenden Studie sollte untersucht werden, welcher Zusammenhang zwischen dem Somatomedin-C als Wachstumshormon und der Aminosäurezusammensetzung im Nabelvenenblut in Bezug auf das fetale Wachstum besteht.
Bei Schwangerschaften am Termin war die Somatomedin-C-Konzentration bei normalgewichtigen Kindern höher als bei Fällen mit fetaler Wachstumsretardierung. Innerhalb der somatischen Parameter wies lediglich das Geburtsgewicht der am Termin entbundenen Kinder eine signifikante, positive Korrelation zum Somatomedin-C-Spiegel im Nabelvenenblut auf. Bezüglich der 40 Aminosäuren und ihrer Abkömmlinge wurde eine signifikante, positive Korrelation zur Somatomedin-C-Konzentration gefunden für: Glutamin, Prolin, Asparagin, Methionin, Isoleucin und Äthanolamin. Eine signifikant negative Korrelation hingegen bestand bei Kindern am Termin zwischen der Tryptophankonzentration und dem Somatomedin-C-Spiegel. Bei Wachstumsretardierung ergaben die Untersuchungen eine signifikant positive Korrelation in Bezug auf das Glutamin und eine signifikant negative Korrelation in Bezug auf das Tryptophan.
Trotz vieler offener Fragen läßt sich aus den Ergebnissen der Studie folgende Hypothese ableiten: Bei der Regulation des fetalen Wachstums in utero besteht ein Zusammenhang zwischen dem Somatomedin-C als wachstumsförderndem Faktor und einigen Tryptophan-Metaboliten, wie z. B. Serotonin und/oder Methionin.

Schlüsselwörter: Aminosäuren, Fetus, Somatomedin-C, Wachstumsfaktor.

Résumé

Somatomédine C comme facteur de promotion de la croissance fœtale et composition en acides aminés du sang du cordon chez les nouveaux-nés japonais
On réalise une étude pour déterminer la relation de la somatomédine C comme facteur de promotion de la croissance avec la composition en acides aminés du sang veineux ombilical en relation avec la croissance fœtale.
Chez les grossesses à terme, la somatomédine C est plus élevée dans les cas où la croissance fœtale est normale que dans les cas avec retard de croissance. Parmi les paramètres cliniques, seul le poids de naissance des enfants à poids normal pour le terme a une relation positive significative avec la somatomédine C au sang du cordon. Parmi les 40 acides aminés et leurs analogues, on a trouvé des corrélations positives significatives pour la glutamine, la proline, l'asparagine, la méthionine, l'isoleucine et l'éthanolamine avec le taux de somatomédine C, alors qu'on a trouvé une corrélation négative significative entre le tryptophane et la somatomédine C chez les enfants avec un poids normal pour le terme. Dans les cas de retard de croissance intra-utérin, l'évaluation de la relation entre acides aminés et somatomédine C a révélé qu'il existe une corrélation positive significative avec la glutamine et une corrélation négative significative avec le tryptophane.
Bien que de nombreux détails au niveau de ces relations ne soient pas clairs, les résultats de ce rapport nous conduisent à spéculer que la somatomédine C en tant que facteur de promotion de la croissance chez le fœtus a certaines relations avec des métabolites du tryptophane, par exemple avec la sérotine et/ou la mélatonine dans la régulation de la croissance fœtale in utéro.

Mots-clés: Acides aminés, facteurs de croissance, fœtus, somatomédine C.

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